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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/258,132	02/26/1999	PHILIP GOELET	04990.0007.U	3407

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/258,132	GOELET ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64 and 66-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64 and 66-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 26, 2006 has been entered.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 64, 66, 67, and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO) 90/11372, October 4, 1990; cited in the IDS).

It is noted that EP 0412883A1 claims priority to application 8910802, which issued as and is identical in content to FR 2,650,840. An English translation of FR 2,650,840 was filed in the IDS of June 8, 1999.

Cohen teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a single-stranded nucleic acid sample with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids present in the sample, wherein the primer hybridizes immediately 3' of the nucleotide to be determined; contacting the duplexes with a solution containing four different terminators, each terminator labeled with a different detectable moiety; extending the primer with the terminator, and determining the identity of the incorporated terminator to thereby determine the identity of the nucleotide base (see pages 4 and 5). Cohen (page 6) states that "if the four blocking bases are marked by means of different markers, the four blocking nucleotides are advantageously detected at the same time." In the method of Cohen, only terminator nucleotides are present in the extension reaction – the reaction does not contain dATP, dCTP, dGTP or dTTP (see, for instance, Example 1). Cohen does not teach performing the primer extension reaction using multiple primers, each comprising a different affinity moiety.

However, Davis teaches a method for determining the identity of one or more nucleotide bases in a nucleic acid molecule wherein the method comprises contacting a single stranded nucleic acid molecule with an oligonucleotide primer to form a duplex between the primer and complementary target nucleic acids; contacting the duplexes with a solution containing labeled dNTPs, labeled with a different detectable moiety; extending the primer with the dNTPs such that if the primer is perfectly complementary with the target nucleic acid, an extension product is formed, but if the primer contains a mismatch at or near the 3' end of the primer, an extension product is not formed, and detecting the presence of an extension product in order to determine the identity of a nucleotide base (see pages 3-4). Davis teaches that the identity of multiple nucleotides can be determined simultaneously by using a mixture of different oligonucleotides, each oligonucleotide comprising a unique tail (i.e., affinity moiety). Following the extension reaction, the primer extension/target nucleic acid complex is denatured, and the primer extension product is hybridized to a solid support having bound thereto sequences complementary to the primer tail. The unique tail allows for the primers to be immobilized at specific locations on the support (see pages 4-5). Davis teaches that the use of multiple primers, with different tail sequences allows for the simultaneous analysis of multiple sequences and improves the speed and sensitivity of the detection method (see page 21).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having a different tail (i.e., each comprising a different affinity

moiety) and to have separated the primer extension products from the reaction medium by contacting the extension products with a solid support having immobilized thereon a capture probe complementary to the tail sequence (i.e., an affinity group complementary to the affinity moiety of the primer) in order to have accomplished the objectives set forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

With respect to claim 66, Cohen teaches that the terminator (or "blocking nucleotide") is a dideoxynucleotide (see page 5). With respect to claim 67, Cohen teaches that the terminator comprises one or more of ddATP, ddCTP, ddGTP or ddTTP (see pages 7 and 8). With respect to claims 69 and 70, Cohen teaches that the terminator may be labeled with a fluorophore, or chromophore, isotope, enzyme or antibody (see page 5).

RESPONSE TO ARGUMENTS:

In the response filed June 26, 2006, Applicants traversed this rejection by stating that the Cohen reference would have led persons skilled in the art away from any technique that required the immobilization of a nucleic acid onto a membrane. The response states that Cohen draws no distinction between reversibly immobilizing nucleic acids on a membrane and irreversibly immobilizing nucleic acids on a membrane, but rather teaches only the general advantage of the method disclosed therein as not requiring immobilization of a nucleic acid on a membrane. Applicants point to page 3 of the Cohen reference as teaching that immobilization of nucleic acids on a membrane is a disadvantage of the method of Southern blotting and the method of

Mundy (U.S. Patent No. 4,656,127). The response states that it is a property of Southern blotting method that in this method a nucleic acid is irreversibly bound to a membrane by vacuum baking or a similar process. The response also states that in the method of Mundy, single-stranded target nucleic acids are bound to a nitrocellulose filter and baked onto the filter. The response points to the teachings of Davis in which an oligonucleotide is spotted onto a substrate. It is argued that such a method is equivalent to irreversibly binding the oligonucleotide to a membrane by baking or a similar process. It is further argued that the ordinary artisan would recognize that the method of Davis is an equivalent technique requiring immobilization of the nucleic acid and that the ordinary artisan would recognize that the method of Davis shared the disadvantages of previously known techniques requiring immobilization onto a membrane. Thereby, Applicants conclude that Cohen teaches away from the "the hypothetical combination."

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection for the following reasons.

First, it is acknowledged that Cohen (page 3) teaches that "By selecting suitable hybridization and rinsing conditions (specific for each system), hybridization by means of marked oligonucleotides can be achieved only in case of perfect equivalence (the difference of a single nucleotide, particularly at the site of the mutation, results in destabilization of the hybridization). However, these various techniques all have a certain number of disadvantages: - the temperature conditions are difficult to master to achieve suitable hybridization; - the mandatory presence of a restriction site may be required; - the nucleic acid is immobilized on a membrane (Southern blot). "

Accordingly, it is acknowledged that Cohen teaches away from using Southern blot hybridization techniques to directly detect single nucleotide variations – **i.e., teaches away from irreversible immobilization of a target nucleic acid prior to probe hybridization.** Cohen teaches away from using this methodology because in this type of a hybridization method in which hybridization of a probe to a target nucleic acid is performed to directly detect a sequence variation in the target nucleic acid, the conditions of hybridization are critical to the accuracy of the assay. Immobilization of the target nucleic acid to a solid support is known to interfere with the kinetics of the hybridization process and thereby with the specificity of hybridization. Again, the criticality of the hybridization process is important here because it is the hybridization step which is relied upon solely to distinguish between nucleic acids having single nucleotide variations.

However, the method of Davis is distinct from that of Southern and Mundy. In the method of Davis, the immobilization of the nucleic acid is not irreversible and it does not occur prior to hybridization. Rather, in the method of Davis, probe hybridization of the target nucleic acid to the primer occurs in solution and the primer extension products are formed in solution. Only after the primer extension reaction has occurred is the primer extension product reversibly immobilized onto a solid support. Immobilization of the primer extension product at this point in the assay does not interfere with the specificity of the detection process because the specificity of the detection process occurs at the steps of primer hybridization (in solution) and primer extension (in solution).

Accordingly, Applicant's interpretation of the teachings of Cohen are taken out of context. Cohen teaches away only from methods of using hybridization to directly detect a sequence variation, and particularly teaches away from the method of Southern blotting to detect a sequence variation. Cohen does not, however, teach away from the method of Davis in which following primer hybridization and extension in solution, the primer extension product is immobilized in order to facilitate the separation of the primer extension product from the reaction components. As set forth by Davis, this methodology provides the advantage of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

Applicants response also states that Davis teaches a method in which oligonucleotides are covalently, irreversibly bound to a substrate. However, these teachings in Davis relate only to the capture oligonucleotides. The capture oligonucleotides are used to immobilize the primer extension product. These teachings are NOT directed to the immobilization of a target nucleic acid, particularly prior to hybridization of a target nucleic acid to a primer or probe, or prior to primer extension. Accordingly, Applicants characterization of the teachings of Davis are also taken out of context. Regarding the capture oligonucleotides, the means by which the capture oligonucleotides are immobilized is not relevant since hybridization of the extension product to these oligonucleotides does not require the specificity that is relied upon to detect the presence of a single nucleotide variation between a target nucleic acid and a probe. Also, the fact that the capture oligonucleotides may be irreversibly bound to a

substrate is not relevant because the capture oligonucleotides do not need to be released from the substrate for further analysis or reuse. Rather, it is the primer extension product which one might want to release from the support. Since the primer extension is immobilized indirectly to the support via hybridization to the capture oligonucleotide, the primer extension product can be released by denaturation in order to allow for the further analysis of the primer extension product and/or re-use of the immobilized capture probes.

It is also important to note that Davis and Cohen are analogous art since both the method of Davis and the method of Cohen rely on performing a primer extension reaction to detect a single nucleotide variation. On the other hand, Cohen and Southern do not rely on similar techniques to accomplish the detection of a single nucleotide variation, since Cohen teaches detecting a single nucleotide variation using a primer extension reaction and Southern teaches detecting a single nucleotide variation using a probe hybridization reaction.

For the reasons stated above, it is maintained that Cohen and Davis when considered as a whole would have lead the ordinary artisan to the claimed invention. As discussed in the above rejection, Davis teaches that the immobilization of primer extension products to a solid support via an affinity moiety allows for the use of multiple distinct primers simultaneously. Thereby, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have used multiple primers, each having an affinity moiety and to have separated the primer extension products from the reaction medium by contacting the

extension products with a solid support in order to have accomplished the objectives set forth by Davis of allowing for the analysis of multiple sequences simultaneously and of providing a more rapid and sensitive means for determining the identity of a nucleotide.

3. Claim 68 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Prober (U.S. Patent NO. 5,332,666).

The teachings of Cohen and Davis are presented above. The combined references do not teach using a terminator that comprises arabinoside triphosphate.

However, Prober teaches methods for determining a nucleotide sequence wherein the method comprises performing a primer extension reaction using a terminator. Prober teaches that the terminator may contain an arabinose as the sugar group and provides a number of examples of terminators comprising an arabinoside triphosphate (see column 18).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cohen so as to have a terminator comprising an arabinoside triphosphate because this would have provided an equally effective terminator for the extension reaction and for determining the identity of a nucleotide in a target nucleic acid.

RESPONSE TO ARGUMENTS:

In the response filed, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

4. Claim 71 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cohen et al (EP 0412883A1 (published February 13, 1991; cited in the IDS) or Cohen et al (FR 2,650,840 (published February 15, 1991; cited in the IDS), each in view of Davis (WO 90/11372, October 4, 1990; cited in the IDS) and Tabor (U.S. Patent NO. 4,962,020; cited in the IDS).

The teachings of Cohen and Davis are presented above. The combined references do not teach including pyrophosphatase in the primer extension medium.

However, Tabor (columns 15-16) teaches including pyrophosphatase in primer extension reactions. The reference teaches that pyrophosphatase removes pyrophosphate which builds up during extension reactions. Specifically, Tabor (column 14) teaches that in the presence of pyrophosphate, DNA polymerase will add pyrophosphate to the 3' terminal nucleotide, causing the release of dideoxynucleoside 5'-triphosphates. As stated by Tabor (column 15, lines 1-2), "This reaction has the effect of removing the block at the 3' terminus."

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Cohen so as to have included pyrophosphatase in the reaction medium in order to have achieved the expected benefit of eliminating pyrophosphorolysis activity of DNA polymerase and thereby reducing the probability that the labeled terminator would be removed and that

unlabeled dideoxynucleotides would be released into the reaction medium. Thereby, the ordinary artisan would have been motivated to have include pyrophosphatase in the extension reaction in order to have ensured the accuracy and sensitivity of the method for determining the identity of a nucleotide.

RESPONSE TO ARGUMENTS:

In the response, Applicants traversed this rejection for the same reasons as set forth in paragraph 2 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)-272-0735.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
Art Unit 1634

CARLA J. MYERS
PRIMARY EXAMINER